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The Treatment of Shock Based Upon Physiological Principles and Impedance Method for Measuring Cardiac Output in Shock

Annual Progress Report

Richard C. Lillehei, M.D., Ph.D.

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ABSTRACT

Using radioactive microspheres, we have found that neither endotoxin nor gram negative bacteria or the combination of the two, when used to induce shock in dogs, cause arteriovenous shunts to open in the gut or the liver. Shunts cannot be demonstrated in the lungs under these same conditions. Inflammation in addition to injection of bacteria and/or endotoxin appears necessary before arteriovenous shunts open. Capillary membrane permeability pressures in shock have been measured in the forepaw of the dog. Shock is associated with a decreased capillary pressure due to leak of fluid through damaged capillary walls. Massive doses of corticosteroids or tolerance to shock induced with epinephrine or endotoxin preserves membrane permeability pressure in the normal range. Tolerance to epinephrine or endotoxin is also associated with decreased reactivity of the renal and intestinal microcirculation during shock. Correlation between laboratory experiments and clinical treatment of shock has been obtained with a portable shock unit.

FOREWORD

In conducting the research described in this report, the investigator(s) adhered to the "Guide for Laboratory Animal Facilities and Care," as promulgated by the Committee on the Guide for Laboratory Animal, Resources, National Academy of Sciences-National Research Council.

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I. Experimental Studies

A. Microcirculation in Septic Shock

Arteriovenous shunting in the viscera of man apparently plays a major role in the hemodynamic and metabolic disturbances occurring in gram negative septic shock. Yet the mechanism for shunting is not fully understood and the existence of shunts is difficult to prove. We have studied shunting in the lung, liver, and intestine of dogs subjected to hemorrhagic, septic, or cardiogenic shock. The septic shock models include injection of endotoxin alone, injection of endotoxin and living Escherichia coli bacteria, and injection of endotoxin, living Escherichia coli bacteria and the creation of an inflammatory focus in the viscera or subcutaneous tissues. Shunting in these shock models was studied by the use of radioactive plastic microspheres (25±5 micra) for the liver and intestine and by the use of arterial and venous oxygen tensions and Berggren's formula of the lung.

The radioactive microspheres are injected into the superior mesenteric artery of dogs following induction of whatever shock is being studied. Blood flow from the superior mesenteric veins is then collected and the number of microspheres passing through the superior mesenteric microcirculation is estimated by measuring the radioactivity of the collected blood. The microspheres passing through the hepatic artery distribution of dogs in shock from various causes are caught in the lungs and the radioactivity of the excised lung is then measured.

Berggren's equation has been used to determine the pulmonary arteriovenous shunting in these same shock models. We have found that the number of microspheres as measured by radioactivity passing through the superior mesenteric or hepatic circulation in dogs in shock from endotoxin or from endotoxin and bacteria, is less than one percent.

The findings in the lung are similar to those for the liver and gut, with no significant increase in pulmonary shunting noted from injection of endotoxin or endotoxins and living bacteria. These studies give further evidence that in sepsis neither endotoxin nor bacteria alone are responsible for the arteriovenous shunting which is so commonly found in man suffering septic shock.

To simulate more closely the septic shock picture of man, we are now developing an experimental septic shock model in the dog, pig, and monkey, which combines the injection of living bacteria, endotoxin, and the creation of a focus of inflammation. In preliminary studies, we have here shown for the first time that we can reproduce the hemodynamic and metabolic changes which are seen in man suffering gram negative sepsis. Our next step is to study the effects of treatment, with special emphasis on massive doses of corticosteroids, on this septic shock model in which high cardiac output and low resistance occurs. Proposals for this study are detailed in the contract application for the years 1969 - 70.

B. Capillary Membrane Permeability

We have studied the capillary membrane permeability pressure of the forepaw of dogs suffering shock due to the endotoxin of Escherichia coli bacteria. This is another attempt to examine the microcirculation in shock and its response to treatment. Using an isolated, isogravimetric forepaw of the dog, we determined the capillary permeability pressure to be 17 mmHg in normal dogs. The capillary permeability pressure of the forepaw four hours following the induction of endotoxin shock decreases to 9.5 mmHg indicating that in endotoxin shock the capillary integrity is damaged and fluid is apparently leaking into interstitial spaces more easily than normal.

The isolated forepaw preparation of the shocked dog treated early with fluids and a massive dose of methylprednisolone retains a capillary permeability pressure in the normal range (about 17 mmHg). This indicates that treatment has apparently stabilized and preserved the integrity of the capillary membrane in the forepaw and, by doing so, has prevented loss of fluid into the interstitial spaces of the forepaw. Thus, these studies show a specific mechanism for the loss of volume in septic shock. Moreover, these studies show another beneficial effect of massive doses of corticosteroids in maintaining the integrity of the capillary membrane. Previously we demonstrated that massive doses of steroids slowed nerve impulse transmission in sympathetic nerves which reduces the intensity of vasoconstriction characteristically occurring in shock.

Similar studies on capillary permeability pressure are now being done on the kidney. Here again, these studies indicate that there is a loss of capillary integrity as evidenced by lowered capillary permeability pressure after septic shock is induced. Treatment with corticosteroids maintains the permeability pressure of the microcirculation of the kidney in the normal range. The model here has been endotoxin induced shock, but similar changes appear to occur in cardiogenic shock and in hemorrhagic shock when it is prolonged. Similar studies are being planned for the pig and for the rhesus monkey to obtain data in experimental animals with a physiology more closely akin to man.

C. Tolerance to Shock

High doses of epinephrine, norepinephrine, and endotoxin result in increased sympathetic nervous activity, peripheral vasoconstriction, reduced tissue perfusion and death of dogs. Given in sublethal amounts, the dosage of these agents can be increased to usually lethal levels without adverse effects if done in a stepwise fashion. The dog is then considered tolerant to one or the other of these substances. Under these conditions, the dogs are relatively insensitive to sympathetic stimulation and do not respond by intense peripheral viscerocutaneous vasoconstriction which is, apparently, the cardinal response to hemorrhagic, septic, and cardiogenic shock.

In tolerant dogs, relatively insensitive to vasoconstrictive stimuli, the induction of usually lethal hemorrhagic, septic, or cardiogenic shock does not result in the usual degree of intensive peripheral vasoconstriction. That is, the alpha adrenergically sensitive viscerocutaneous vascular beds do not respond by vasoconstriction despite a fall in cardiac output and blood pressure. Thus, blood flow remains more equitably distributed to all vascular beds. Moreover, oxygen consumption remains in the normal range and survival is near 100 percent.

Capillary permeability studies have been started on tolerant dogs in shock. These indicate that induced tolerance to shock, like massive doses of corticosteroids, preserve a more normal capillary pressure, indicating that one means by which tolerance to shock protects against death is through preservation of capillary integrity.

We have found that induction of tolerance by the use of chronic injections of epinephrine norepinephrine, or endotoxin, in sublethal amounts, can usually be induced in a minimum of two weeks. The tolerance so induced appears to last for up to three months, but is definitely dissipated by six months. Tolerance studies are now planned for the pig and for the rhesus monkey as the next step in the eventual induction of tolerance to shock in man. This program has great eventual benefits for the combat soldier as well as to civilians exposed to military or natural catastrophes.

II. Clinical Shock Unit Patients

A. General Plan of Observation and Treatment

During the past year, 1968-69, we have studied 85 patients in shock at the University of Minnesota Hospitals, with the aid of our clinical shock unit. While these studies are not directly supported by the Research and Development Command contract, the results of these studies provide evidence of the value of applying the principles learned in the laboratory to the treatment of the acutely ill.

These patients who suffered from traumatic, cardiogenic or septic shock, or combinations of these problems were studied with the aid of a mobile shock cart equipped with strain gauge transducers, a transistorized densitometer, and other equipment allowing us visual readout of arterial and venous pressures, cardiac outputs, and other derived data for immediate use at the bedside. Such data is also recorded for future use. In addition to hemodynamic studies, respiratory and metabolic effects of shock are also recorded. Arterial and venous oxygen and carbon dioxide tensions and saturations are measured. Most patients are also being assisted with one of the various types of respirators so oxygen uptake can be measured and, ultimately, oxygen consumption determined. Moreover, with the aid of Berggren's formula and the above data, arterial venous shunting in the lungs can be estimated. Blood pH, and lactate, and serum electrolytes are also measured and used as a guide to treatment. All patients are also catheterized so that hourly urine volumes can be accurately recorded. All of the above data, including a careful examination of the patient are available within 30 to 45 minutes after the patient in shock is seen.

B. Hemodynamic Observations in Septic Shock

A constant finding in patients suffering actual or impending septic shock is a normal or high cardiac output along with a normal or low total peripheral resistance. These findings occur in the face of clinical signs of poor nutritional blood flow such as acidosis, elevated blood lactate, oliguria, and cool, pale, skin.

The desparity between clinical signs of shock and hemodynamic measurements of an apparently adequate cardiac output can only be explained by the opening of arteriovenous shunts. These can be most easily demonstrated in the lung, where we find that oxygen tension of arterial blood is usually below normal even though the patient is receiving 100 percent oxygen. Moreover, the low arterial venous oxygen difference suggests that blood is bypassing nutritional vascular beds not only in the lung, but in the other viscera and skin as well. These shunts can exist in the lung, in the viscera, in inflammed pleura, or peritoneum, or subcutaneous tissues. Attempts to measure shunting directly in septic shock in the kidney have begun by placing catheters in the renal artery and renal vein of patients in shock. Here again, using the oxygen saturations, and blood flow studies across this organ, we believe we can obtain blood flows across the kidney as well as data to indicate whether shunting is present in this organ in sepsis.

The living bacterial factors seem responsible for the opening of shunts since endotoxin in the absence of bacterial inflammation in the dog does not lead to shunting in any organ as was noted above. However, when an inflammatory process is induced by chemicals or bacteria along with endotoxins, we then can reproduce the picture which is so characteristically seen in man of a high cardiac output and low total peripheral resistance in the face of a severe decrease in nutritional blood flow to the viscera and skin.

The therapeutic protocol for the patients in septic shock includes liberal use of blood, plasma, plasma substitutes, low molecular dextran, and balanced salt solutions, combined with massive intravenous doses of corticosteroids, usually methylprednisolone (30 mg/kg) or dexamethasone (6 mg/kg). Along with these measures, synthetic penicillins, and kanamycin are given intravenously. Finally, the source of bacterial contamination is eliminated whenever possible. This combination of measures has lead to the survival (actual discharge from the hospital) of over 70 percent of the patients, a notable improvement in our own previous results and in the results reported by others.

C. Cardiogenic Shock

A protocol similar to that outlined above for those patients suffering septic shock has been used with success in cardiogenic shock in which the increased peripheral resistance of cardiogenic shock is decreased by the use of massive doses of corticosteroids. The use of vasopressor substances has been avoided in most patients.

D. Impending Shock

In the past year, we have been called earlier to see patients who are suffering sepsis or cardiovascular problems. Many of these patients still have a normal blood pressure, although they manifest signs of a low cardiac output, and high resistance with oliguria if cardiac damage is the problem. Other patients suffering sepsis show the typical signs of high cardiac output and low resistance with oliguria. When these patients are seen early and treated early with fluids and massive doses of corticosteroids, then subsequent hypotension has not occurred and survival is near 100 per cent. It is our hope that the prevention of shock through the eventual induction of tolerance in man combined with early treatment may virtually eliminate death from septic or cardiogenic insults or following trauma.

III. Impedance Method for Measuring Cardiac Output in Shock

A separate report has been submitted on this phase of our study by Dr. Robert Ersek.

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Richard C. Lillehei, M.D., Ph.D. William G. Kubicek, Ph.D.
George J. Motsay, M.D.
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